Medicine Cabinet

Management of uncomplicated urinary tract infections

Timothy Jancel
Vicky Dudas

Department of Clinical Pharmacy
University of California, San Francisco, Medical Center
521 Parnassus Ave, Room C-152
San Francisco, CA 94143-0622

Correspondence to:
Dr Jancel
tjancel@itsa.ucsf.edu

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Summary points

- In the past decade, resistance of uropathogens to trimethoprim-sulfamethoxazole and trimethoprim has increased dramatically
- Three-day therapies appear to be optimal and provide similar eradication rates and a lower incidence of side effects than 7 to 10 days of therapy
- Trimethoprim-sulfamethoxazole and trimethoprim are still considered first-line therapy for uncomplicated urinary tract infections in areas where resistance in the community is less than 10% to 20%
- Fluoroquinolones should not be used as first-line drug therapy except in communities wherein resistance to trimethoprim is greater than 10% to 20% or in patients with risk factors for resistance
- In patients who have frequent bouts of recurrent uncomplicated cystitis, antibiotic prophylaxis should be offered to prevent infections

Uncomplicated urinary tract infections are among the most frequently occurring infections in the United States, resulting in an estimated 8 million office visits and 1 million hospital admissions each year.[1-3] Between 40% and 50% of women have reported having at least one urinary tract infection in their lives.[4]

Urinary tract infections can be classified by anatomic site of involvement into lower and upper urinary tract infections. Infections of the lower urinary tract include cystitis, urethritis, prostatitis, and epididymitis, and those of the upper urinary tract include pyelonephritis. Urinary tract infections may be further classified as complicated or uncomplicated. In women with a structurally and functionally normal urinary tract, cystitis and pyelonephritis are considered uncomplicated urinary tract infections. Urinary tract infections in men, elderly people, pregnant women, or patients who have an indwelling catheter or an anatomic or functional abnormality are considered complicated urinary tract infections. In this article, we outline the pharmacologic approach to the prevention and treatment of uncomplicated cystitis.

ETIOLOGY

Risk factors for urinary tract infections in women include frequent sexual intercourse, lack of urination after intercourse, use of a diaphragm, use of a spermicide, and a history of recurrent urinary tract infections.[5,6] Although the long-term adverse effects associated with uncomplicated urinary tract infections appear to be minimal, if left untreated, urinary tract infections can interfere with daily living. As many as 80% of uncomplicated urinary tract infections are caused by *Escherichia coli*, followed by *Staphylococcus saprophyticus* in as many as 5% to 15% of cases. Enterococci, *Klebsiella* species and *Proteus mirabilis* account for a small percentage of overall infections.[7]

OVERVIEW OF ANTIBIOTICS

The antimicrobial agents most commonly used to treat uncomplicated urinary tract infections include the combination drug trimethoprim and sulfamethoxazole, trimethoprim, β-lactams, fluoroquinolones, nitrofurantoin, and fosfomycin tromethamine. These agents are used primarily because of their tolerability, spectrum of activity against suspected uropathogens, and favorable pharmacokinetic profiles.[8] In the treatment of urinary tract infections, the resolution of bacteriuria has been correlated with the concentration of the antimicrobial agent in the urine rather than serum levels.[9] All the antimicrobial agents approved for the treatment of urinary tract infections achieve inhibitory urinary concentrations that significantly exceed serum levels. Also, agents such as trimethoprim-sulfamethoxazole or the fluoroquinolones that eradicate aerobic gram-negative flora but have little effect on the vaginal and fecal anaerobic flora seem to provide the best long-term cures for uncomplicated urinary tract infections.[8]

Resistance to antibiotics

Because most uncomplicated urinary tract infections are treated empirically, it is important for clinicians to recognize resistance patterns of uropathogens in the community to ensure that the most appropriate antimicrobial agent is chosen. Recent reports have demonstrated that the emergence of resistant uropathogens has had a tremendous effect on empiric therapy.[7,10-13] The most dramatic increase in resistance in the past few years has been to trimethoprim-sulfamethoxazole. A recent study that evaluated outpatient women aged 18 to 50 years in the Seattle area who had acute cystitis demonstrated that the prevalence of *E coli* resistance to trimethoprim and trimethoprim-sulfamethoxazole rose from 9% to 18% in 1992 and 1996, respectively. This study also showed that the resistance of *E coli* to β-lactams such as ampicillin and first-generation cephalosporins was 34% and 28%, respectively.[10] To further delineate resistance in geographic regions, a national survey was conducted to analyze antimicrobial susceptibilities of urine isolates from female outpatients in 1998. The highest percentage of resistance to *E coli* (22%) was seen in the western United States

(California, Oregon, and Washington), in contrast to the Northeast where resistance was lowest (10%).[12] To date, *E coli* resistance to the fluoroquinolones and nitrofurantoin appears to be relatively low.[12,14]

What effect does resistance have on empiric therapy? A committee of the Infectious Disease Society of America recently reviewed the literature on antimicrobial therapy for uncomplicated acute bacterial cystitis and pyelonephritis in woman. The guidelines recommend trimethoprim or trimethoprim-sulfamethoxazole as first-line empiric therapy *only* in communities where resistance to trimethoprim among the uropathogens is less than 10% to 20%.[15]

TREATMENT

The goal of antimicrobial therapy is to eliminate the infecting organisms from the urinary tract and provide the resolution of symptoms. Table 1 lists the drugs, their dosages, and wholesale costs. Clinicians should consider many factors when selecting an antibiotic for a urinary tract infection, such as the patient's allergy history, the cost and tolerability of the treatment, previous antibiotic therapy, and most important, the prevalence of resistance in the community.

Single-dose regimens

Although single-dose therapy using β-lactams, trimethoprim-sulfamethoxazole, trimethoprim, and fluoroquinolones have shown high cure rates, single-dose therapy is associated with a high rate of recurrence within 6 weeks of initial treatment. Reinfection may be due to the failure of single-dose treatment to eradicate gram-negative pathogens from the perianal area. Aminopenicillins and first-generation cephalosporins have shorter half-lives, which may contribute to their lower efficacy compared with other agents.[16,17] The 1999 treatment guidelines of the Infectious Disease Society of America on uncomplicated urinary tract infections concluded that multiple-day regimens were more effective than single-dose regimens, especially for the aminopenicillins and first-generation cephalosporins.[15] Single-dose therapy offers the advantages of increased compliance and a lower incidence of side effects.

Table 1 *Antibiotic therapy for urinary tract infections*

Drug	Dose, mg	Frequency	Duration, days	Cost per complete course, $*
Sulfonamides				
TMP-SMX	160/800†	2×/day	3	6.30-8.80
TMP	100	2×/day	3	0.90-1.40
Fluoroquinolones				
Norfloxacin (Noroxin)‡	400	2×/day	3	22.80
Ciprofloxacin HCl (Cipro)‡	100-250	2×/day	3	17.20-25.00
Levofloxacin (Levaquin)‡	250-500	Daily	3	21.90-25.60
Nitrofurantoin macrocrystals				
(Macrodantin)‡	100	4×/day	7	47.00
(Macrobid)‡	100	2×/day	7	23.00
β-Lactams				
Cefpodoxime (Vantin)‡	100	2×/day	3	18.30
Cefixime (Suprax)‡	400	Daily	3	23.20
Cephalexin	250-500	4×/day	3	6.40-11.50
Amoxicillin	250-500	3×/day	3	2.10-3.50
Miscellaneous				
Fosfomycin tromethamine (Monurol)‡	3,000 (3 g)	Daily	1	30.00

TMP-SMX = trimethoprim-sulfamethoxazole; HCl = hydrochloride.
*Average wholesale price in 2001.
†One double-strength tablet.
‡Proprietary names are given for information only and are not to be construed as endorsement by either the authors or *wjm* editors.

Short-course therapy

Controlled trials of uncomplicated urinary tract infections have demonstrated that therapy for 3 days provided similar eradication rates and a lower incidence of side effects compared with 7 to 10 days of therapy.[17-19] The guidelines of the Infectious Disease Society of America also concluded that 3-day regimens of trimethoprim, trimethoprim-sulfamethoxazole, and fluoroquinolones were more effective than single-dose regimens and that single- or 3-day regimens were better tolerated than longer regimens (7-10 days). Patients who may require 7 days of therapy include pregnant women, patients with diabetes mellitus, and those with symptoms lasting longer than 1 week.[15] For uncomplicated cystitis, treatment with trimethoprim-sulfamethoxazole, trimethoprim, or fluoroquinolones for 3 days should result in an eradication rate of greater than 90% with a low incidence of adverse effects.

RECURRENT URINARY TRACT INFECTIONS

Patients with three or more infections per year should be offered either continuous low-dose antibiotic prophylaxis, patient-initiated, or postcoital prophylaxis if the onset of infection is linked to sexual intercourse (table 2).[7] Before a prophylactic regimen is chosen, a urine culture should be performed to determine the susceptibility of the pathogen. The duration of continuous prophylactic therapy is usually 6 months to a year. Unfortunately, within 6 months of discontinuing antibiotic prophylaxis, 40% to 60% of women develop a urinary tract infection, and prophylaxis must be resumed.[20] Patient-initiated therapy at the onset of symptoms has been shown to be effective in young, healthy nonpregnant women.[21] Short-course regimens (as previously described) have been advocated for patient-initiated therapy in compliant women with frequently recurring and symptomatic urinary tract infections. The major advantages of short-course therapy over continuous therapy are convenience and the avoidance of antibiotic

Table 2 *Antibiotic prophylaxis regimens for recurrent infections*

Drug	Dosage
Continuous daily prophylaxis for 6 mo	
TMP-SMX	40/200 mg* nightly or 3×/wk
TMP-SMX	100 mg nightly
Nitrofurantoin	50-100 mg nightly
Norfloxacin	200 mg a day
Cephalexin	250 mg a day
Postcoital prophylaxis†	
TMP-SMX	40/200 mg*
Nitrofurantoin	50-100 mg
Cephalexin	250 mg

TMP-SMX = trimethoprim-sulfamethoxazole.
*Half of a single-strength tablet.
†Must be temporal in nature.

toxicity; symptomatic infections are not prevented, however. For postcoital prophylaxis, nitrofurantoin, trimethoprim-sulfamethoxazole, or fluoroquinolones taken within 2 hours after sexual intercourse have been shown to significantly reduce the incidence of recurrent cystitis.[22,23]

Antimicrobial agents

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole has long been considered the standard of therapy for acute and recurrent urinary tract infections because of its activity against the most common uropathogens and its low cost and tolerability. The synergistic combination of trimethoprim and sulfamethoxazole works at two separate steps of the bacterial folate metabolism, resulting in the inhibition of DNA synthesis.

Patients with a sulfa allergy can receive trimethoprim alone because studies showed a similar cure rate as with trimethoprim-sulfamethoxazole. The most common side effects occurring in about 3% to 5% of patients are skin rash, nausea, and vomiting. More serious side effects such as anemia and Stevens-Johnson syndrome are rare, but patients should always be monitored for their occurrence. Trimethoprim-sulfamethoxazole should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency or renal and hepatic impairment. The serum glucose-lowering effect of sulfonylureas (such as glipizide) may be enhanced by trimethoprim-sulfamethoxazole. Because the use of trimethoprim-sulfamethoxazole may increase the risk of bleeding in patients taking sodium warfarin, the coadministration of these agents should be closely monitored.

Fluoroquinolones

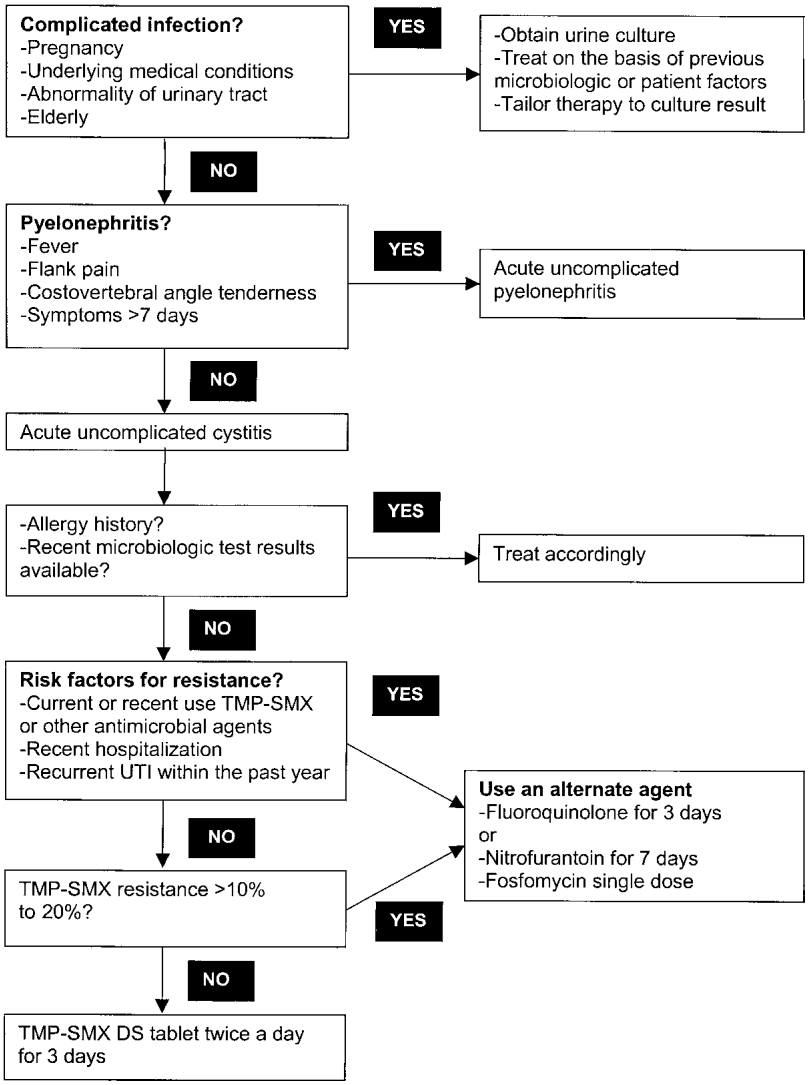
The fluoroquinolones are broad-spectrum antibiotics that inhibit topoisomerase II (DNA gyrase) and topoisomerase IV. Although the spectrum of activity varies among the fluoroquinolones, they all have good to excellent activity against the clinically important gram-negative uropathogens, other Enterobacteriaceae, and *S saprophyticus*. Ciprofloxacin and levofloxacin are the two most commonly used fluoroquinolones for urinary tract infections and cause minimal side effects such as nausea, diarrhea, dizziness, photosensitivity, and headache. Products that contain cations such as magnesium, aluminum, calcium, iron, zinc, or multivitamins with minerals may significantly decrease the absorption of the fluoroquinolones from the gastrointestinal tract. Patients should be advised to take fluoroquinolones 2 hours before or 4 hours after ingesting any product containing cations. Ciprofloxacin and levofloxacin may decrease the metabolism of caffeine and theophylline. Because the coadministration of warfarin and a fluoroquinolone may result in increased anticoagulation, patients taking this combination should be monitored. The use of fluoroquinolones is contraindicated in women who are pregnant or breastfeeding.

Not all fluoroquinolones can be used for urinary tract infections based on their pharmacokinetic profiles. Sparfloxacin and moxifloxacin achieve considerably lower concentrations in the urine than other quinolones and are not approved for this indication. Although the 8-methoxyquinolones, gatifloxacin and moxifloxacin, have an expanded spectrum of activity that includes improved anaerobic and gram-positive activity, they do not have any benefit in the treatment of urinary tract infections.

β-Lactams

In the past, β-lactam antibiotics such as first-generation cephalosporins (cephalexin) and the aminopenicillins (ampicillin, amoxicillin) were routinely used to treat urinary tract infections. Although the first-generation cephalosporins and the aminopenicillins achieve high urinary concentrations, they are no longer recommended as first-line therapy for urinary tract infections because of resistance and higher recurrence rates compared with other agents.[15] These agents should be used only if a urine culture documents susceptibility. However, third-generation cephalosporins such as cefixime and cefpodoxime offer the advantage of longer half-lives, which allows for less frequent dosing. Also, lower resistance rates to *E coli* have been observed with these agents than with the first-generation cephalosporins and aminopenicillins. These agents may be options for patients who are intolerant to trimethoprim-sulfamethoxazole or who have resistant infections.

The most common side effects of the β-lactams include rash, nausea, abdominal pain, vomiting, and headache. The β-lactams inhibit bacterial wall synthesis. The use of cephalosporins and penicillins should be avoided in patients with a history of serious β-lactam allergy (anaphylaxis, hives).



Algorithm for the treatment of uncomplicated urinary tract infections (adapted from Gupta et al[13] and used with permission). TMP-SMX = trimethoprim-sulfamethoxazole; UTI = urinary tract infection; DS = double-strength.

Nitrofurantoin

Nitrofurantoin is available in two formulations, the macrocrystalline formulation (Macrodantin) and the monohydrate-macrocrystal form (Macrobid). Nitrofurantoin inhibits several bacterial enzyme systems involved with metabolism and possibly inhibits cell wall synthesis. Macrodantin requires dosing every 6 hours whereas Macrobid requires only twice-a-day dosing. About 90% of nitrofurantoin is renally excreted through glomerular filtration and tubular secretion. If the patient's estimated creatinine clearance is less than 0.83 mL per second (<50 mL per minute), antibacterial concentrations attained in the urine are inadequate; therefore, this drug should not be used. Side effects are minimal and may include malaise, cough, and dyspnea. Pulmonary fibrosis is rare and usually associated with therapy for longer than 6 months.

Fosfomycin tromethamine

Fosfomycin is a phosphoric acid derivative used only for the treatment of uncomplicated urinary tract infections. It is administered as a one-time 3-gram oral dose. Fosfomycin inhibits pyruvyl transferase, which is an enzyme that catalyzes the first step in bacterial wall synthesis. Fosfomycin's spectrum of activity includes *E coli*, enterococci, and *Serratia*, *Enterobacter*, *Citrobacter*, and *Klebsiella* species but does not cover *S saprophyticus*. Fosfomycin is available as a powder that must be mixed with 3 to 4 oz of water before oral administration. Overall, it is well tolerated. Side effects that may occur include diarrhea (9%), nausea, vomiting, and esophageal discomfort.

SUMMARY

Trimethoprim-sulfamethoxazole or trimethoprim should be used as first-line therapy because of its low cost and efficacy for uncomplicated urinary tract infections in women *unless* the prevalence of resistance to these agents among uropathogens in the community is greater than 10% to 20%. The fluoroquinolones are more expensive, broader in spectrum, and therefore, should be reserved for communities with rates of resistance to trimethoprim of greater than 10% to 20% or in patients who either cannot tolerate trimethoprim-sulfamethoxazole or have recurrent urinary tract infections. Other options include a 7-day course of nitrofurantoin or a single dose of fosfomycin. The use of first-generation cephalosporins or aminopenicillins is generally not recommended because of high levels of resistance and recurrence. Although resistance to the third-generation cephalosporins is lower than to the first generation, these agents are considered third-line agents because of their cost and efficacy.

In an excellent review article, Gupta and others outlined the treatment of uncomplicated urinary tract infections in women (see Figure).

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